REMARKS

Claims 19-34 are currently pending in the present application. Claims 35 and 36 have been cancelled without prejudice or disclaimer. Claims 19-31 are under examination on the merits. The Examiner has withdrawn claims 32-34 from consideration as being directed to a non-elected invention. Claim 19 is the only independent claim.

For clarity, without prejudice or disclaimer, claims 19-24, 27, 28 and 32-34, have been amended. As discussed below under "Claim Objections" and "Claim Rejections-35 USC §112," Applicants respectfully submit that the amendments made herein are supported by the specification and the original claims and introduce no new subject matter. No additional claim fees are necessitated. Entry of the amendments made herein is proper and respectfully requested.

Claim Objections

Claims 20-24 are objected to because of the use of "a" in the claims.

Claims 20-24 have been amended to replace "a" with "the" as suggested by the Examiner. Withdrawal of the claim objections is respectfully requested.

Claim Rejections 35 USC §112

Claim 19-31 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement.

The phrases "mammary gland-specific signal peptide" and "lacking innate signal peptide" in claim 19 are rejected as new matter.

The phrase "mammary gland-specific signal peptide" has been replaced with "milk-specific signal peptide." Support for "milk-specific signal peptide" is found at page 10, line 21, to page 11, line 4, of the specification. The phrase "lacking innate signal peptide" has been deleted, which renders the new matter rejection of the phrase moot.

A phrase "mature polypeptide of" has been inserted immediately in front of "a B-domain deleted human clotting factor VIII (FVIII) polypeptide" in claim 19. Support for the amendment is found at least from the original claims 1 and 3 and throughout the specification. The "milk-specific signal peptide" is used for best secretion efficiency of a non-mammary protein in the mammary gland, see page 10, lines 23 and 24. The "milk-specific signal peptide" necessarily replaces the signal peptide sequence that is naturally or innately associated with the non-

mammary protein, e.g., the "B-domain deleted human clotting factor VIII (FVIII) polypeptide." Therefore, the "B-domain deleted human clotting factor VIII (FVIII) polypeptide" recited in claim 19 is a mature polypeptide that lacks any signal peptide naturally or innately associated with it.

Accordingly, withdrawal of the new matter rejection, in so far as it may apply to the amended claim 19 and its dependent claims, is respectfully requested.

Claims 20-24 have been amended to replace "a" with "the" as suggested by the Examiner. Withdrawal of the rejection of claims 20-24 for lack of an adequate written description is respectfully requested.

Claim 27 has been amended to recite "up to about 50 mg" instead of "about 50 mg," as supported by original claim 16. Withdrawal of the rejection of claim 27 for lack of an adequate written description is respectfully requested.

Claim 28 has been amended to replace "as the non-human transgenic mammal" with "as the embryo" as suggested by the Examiner. Withdrawal of the rejection of claim 28 for lack of written description is respectfully requested.

Indefiniteness

Claims 19-31 are rejected under 35 USC §112, second paragraph, as being indefinite.

The phrase "lacking its innate signal peptide" has been deleted from claim 19. The deletion renders the indefiniteness rejection of claim 19 moot.

Claim 24 has been rejected, because SEQ ID NO:15 allegedly more accurately further limits the B-domain deleted human clotting factor VIII polypeptide, not the recombinant polypeptide. Applicants respectfully submit that SEQ ID NO:15, as shown by its amino acid sequence, comprises the αS1-casein signal peptide sequence, an exemplary milk-specific signal peptide, and the B-domain deleted human clotting factor VIII (FVIII) polypeptide. Thus, SEQ ID NO:15 more accurately further limits the recombinant polypeptide, not the B-domain deleted human clotting factor VIII polypeptide. Amino acid residues 1-15 of SEQ ID NO:15 are identical to the αS1-casein signal peptide sequence shown in SEQ ID NO:14. Amino acid residues 18-1448 of SEQ ID NO:15 are identical to the B-domain deleted human clotting factor VIII (FVIII) polypeptide. Withdrawal of the indefiniteness rejection of claim 24 is respectfully requested.

Claim 27 has been amended to recite "up to about 50 mg" instead of "about 50 mg." Withdrawal of the indefiniteness rejection of claim 27 is respectfully requested.

Claim 28 has been amended to replace "as the non-human transgenic mammal" with "as the embryo" as suggested by the Examiner. Withdrawal of the indefiniteness rejection of claim 28 is respectfully requested.

Claim Rejections for Obviousness

The Examiner has rejected various claims under 35 USC §103(a) as being unpatentable over the combination of various prior art references.

Reconsideration and withdrawal of the rejection and allowance of the pending claims are respectfully requested, particularly in view of the simultaneously filed Dr. Chen's Declaration, for the following reasons.

As stated in Dr. Chen's Declaration, the Applicants were the first to have actually successfully generated transgenic non-human mammals that secret the B-domain deleted human FVIII polypeptide in milk when the mammals are lactating. None of the cited prior art references describes the successful making of such mammals. The prior art does not provide an enabling disclosure with a reasonable expectation of success.

Also, according to Dr. Chen's Declaration, the presently claimed transgenic mammals provide superior and unexpected results over the prior art, thus would not have been obvious over the prior art.

The presently claimed transgenic mammals secreted BDD-rFVIII into the milk at a high yield. The average concentration of the secreted BDD-rFVIII in milk was about 50 μg/ml, which is about 250-fold more concentrated than that of the normal human plasma. As shown in Supplement Table 1 in Dr. Chen's Declaration, the concentration of the secreted BDD-rFVIII was higher than that of the secreted full-length rFVIII reported in the prior art.

Unexpectedly, it was also discovered that the BDD-rFVIII secreted in the milk of the transgenic mammals also had increased clotting activity. Chen, *Transgenic Research*, 11:257-268, 2002 (Chen"), discloses that "only 5-10% of biological activity of recombinant hFVIII protein produced by transgenic mammary gland was detected by clotting assay as compared with ELISA protein quantification" (page 265). A reference cited at page 241 of Soukharev, *Blood Cells, Molecules and Diseases*, 28:234-248, 2002 ("Soukharev") also recognizes the lower activity of transgenic hFVIII protein in milk due to FVIII interaction with milk proteins. As

shown in Supplement Table 2 in Dr. Chen's Declaration, based on the clotting activity of BDD-rFVIII protein detected in milk of the transgenic mammary glands, about 10-15% biological activity was detected for the BDD-rFVIII protein secreted in milk compared with ELISA protein quantification. This is unexpected, because none of the prior art references has suggested that the use of BDD-rFVIII would not only increase the yield, but also improve the clotting activity, of rFVIII in the milk.

The cited prior art references do not render the present claims obvious, further because the BDD-rFVIII construct used in transgenic mammals of the present application is different from those used in the cell line expression systems in the prior art. As stated in Dr. Chen's Declaration, there was no need to modify the signal sequence for the BDD-rFVIII protein in constructs for the cell line expression systems. The native 19-aa secretion signal peptide of the human FVIII is sufficient to direct the secretion of the BDD-rFVIII protein in the cell line expression systems. However, in constructs used for transgenic mammals, the native 19-aa secretion signal peptide of the human FVIII must be replaced by a milk-specific signal sequence, such as bovine α-S1 casein signal peptide or the bovine α-LA signal peptide, to allow efficient secretion of the BDD-rFVIII protein into mammary glands. In addition, as shown in Supplement Table 3 in Dr. Chen's Declaration, a new recombinant splice site or fusion junction, S741-link to-L1643 of the amino acid sequence of the full length human FVIII, was used for more complete B-domain deletion sequence in the present construct. This new recombinant splice site is not described or suggested by any of the prior art.

Applicants therefore respectfully request that the rejections under 35 USC §103(a) over the prior art references be withdrawn.

Applicants respectfully submitted that claims 19-31 are in condition for allowance and such action is respectfully requested.

Because claims 32-34 depend from and include all elements of claim 1, Applicants respectfully request the rejoinder of claims 32-34 for substantive examination upon the finding of allowability of claim 1. The allowance of claims 32-34 is also respectfully requested based on the finding of allowability of claim 1.

Respectfully submitted,

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Declaration of Chuan-Mu Chen Under 37 C.F.R. § 1.132